

REMARKS

The Present Invention

The present invention provides for novel heterocyclic dihydropyrimidine compounds, pharmaceutical compositions containing such compounds and methods of using such compounds as inhibitors of ion channel function.

Amendments to the Claims

New claims 86-90 have been added. New claims 86-90 are directed to compounds of the present invention that are effective as inhibitors of ion channel function. Claims 61, 66, 69, 70 and 73-79 have been amended to claim subject matter that applicants believe satisfy the statutory requirements for allowance. Claims 61, 62, 66, 69, 70 and 73-79 have been amended to exclude non-elected subject matter. Claims 82 and 84 have been amended to indicate a change in dependency and address a Section 112 rejection, respectively. The new claims and amendments change dependency and/or contain matter that may be found in the specification as originally filed, for example, at page 11, line 5 to page 13, line 14, the Examples and the original claims. Accordingly, no new matter has been added by way of the aforesaid new claims and amendments.

The Pending Claims

Claims 61-63, 66-79 and 81-90 are now pending in this application. Claims 64, 65 and 80 have been withdrawn from consideration in view of a restriction requirement. Claims 61-63, 66-79 and 81-90 provide for novel heterocyclic compounds, pharmaceutical compositions containing such compounds and methods of using of such compounds as inhibitors of ion channel function.

The Office Action

In the Final Office Action dated April 25, 2005, the following rejections are indicated:

1. Claims 69-77 and 79 stand rejected under 35 U.S.C. §112, first paragraph, for allegedly being non-enabling;
2. Claims 61-63, 66-69 and 84 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated;
3. Claims 61-63, 66-69 and 81-85 stand rejected under 35 U.S.C. §103(a) for allegedly being unpatentable in view of the prior art;

4. Claims 61-63, 66-69, 81-83 and 85 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting; and
5. Claim 84 stands rejected under 35 U.S.C. §112, second paragraph, for allegedly being indefinite.

Rejections under 35 U.S.C. §112, first paragraph

Claims 69-77 and 79 stand rejected under 35 U.S.C. §112, first paragraph, for allegedly being non-enabling for failing to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention in scope with the claims. The Office Action contends on page 3 that the specification while enabling for treating atrial arrhythmias does not provide reasonable enablement for treatment of all other diseases of the instant claims.

Applicants respectfully traverse the rejection and submit that given the disclosure in the application and the state of the art one of ordinary skill in the art will be able to make or use the present invention without undue experimentation.

The Office Action contends on page 3 that the references cited by the applicant in applicants' response to the Office Action dated June 16, 2004 filed on December 16, 2004, which is incorporated herein, do not provide enabling disclosure because the references have publication dates ranging from 1999-2004 and that, in order to be considered state of the art, the references' publication dates have to be prior to the filing date of the application. While it is noted that some of the references cited by the applicant in applicants' response to the Office Action dated June 16, 2004 filed on December 16, 2004 have publication dates after the filing date of the instant application, applicants respectfully submit that that these references along with the references that have publication dates prior to the filing date of the instant application, for example, Koh et al., which published on March 1, 1999, Rho et al., which published in November 1999, Coleman et al., which published in August 1999, evidence the high level of skill and predictability as to determining the therapeutic effect of chemical compounds such that one skilled in the art could easily extrapolate the disclosed or known results to the claimed invention without undue experimentation. As further evidence of the high level of skill and predictability as to determining the therapeutic effect of potassium channel inhibitors, for example, their use in treating gastrointestinal disorders and inflammatory or immunological diseases, applicants respectfully

submit herein U.S. Patent 6,194,458, which was filed on October 21, 1999 and claims priority to provisional application 60/106,422, which was filed on October 30, 1998.

In addition, the Office Action has cited several references, including some references submitted by applicants to date, in support of the proposition that some experimentation would be involved for the chemical compound to be used in the treatment of the disorder. Even allowing that some experimentation may be necessary, the fact some experimentation may be conducted does not mean that such experimentation rises to the level of "undue". It is incumbent upon the U.S.P.T.O. to provide evidence that the experimentation needed is undue. However, to date, applicants respectfully submit that no such evidence has been provided.

Because one skilled in the art would be able to make and use the present invention without undue experimentation and the Examiner has not provided any evidence to the contrary, applicants respectfully request that this section 112, first paragraph, rejection be withdrawn.

Rejections under 35 U.S.C. §102

Claims 61-63, 66-69 and 84 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Tsuda et al. (European Patent EP 0217142). As indicated in applicants' Response to Office Action filed on December 16, 2005, which is incorporated herein as if set forth at length, applicants respectfully traverse the rejection and request withdrawal of the Section 102(b) rejection because the cited reference is inapt as Section 102 art in that the compounds listed in the patent specification fail to disclose each and every element of the invention as hereby claimed in the amended claims.

The Office Action contends on page 5 that compound no. 99 of Tsuda et al. wherein the substituent analogous to R^{3*} is $-\text{CO}-\text{NHCH}(\text{CH}_3)_2$ falls within the genus of the instant claims because $-\text{CH}(\text{CH}_3)_2$ can be considered a substituted alkyl within the meaning of Z^{5*} when Z^{6*} is H. Furthermore, the Office Action contends on page 5 that compound no. 156 of Tsuda et al., which is excluded from claim 61, falls within the limitations of claim 84 when R^{5*} and R^{6*} together form an unsubstituted piperidinyl. Assuming *arguendo* that the Office Action accurately describes compounds 99 and 156 of Tsuda et al., applicants' presently claimed compounds as claimed in the amended claims differ from the Tsuda et al. compounds and therefore are not anticipated by the compounds. In applicants' compounds of formula I* as hereby claimed in the amended claims, R^{5*} is not substituted alkyl when R^{6*} is H and R^{5*} and R^{6*} together do not form an unsubstituted piperidinyl.

Accordingly, applicants respectfully submit that the Tsuda et al. reference does not anticipate the present invention because it does not disclose each and every element of the invention as hereby claimed in the amended claims, and this rejection should be withdrawn.

Rejection under 35 USC § 103

Claims 61-63, 66-69 and 81-85 stand rejected under 35 U.S.C. §103(a) for allegedly being unpatentable over Tsuda et al.. As indicated in applicants' Response to Office Action filed on December 16, 2005, which is incorporated herein as if set forth at length, applicants respectfully traverse the Section 103 rejection on the grounds that the Office Action has not established a proper *prima facie* case of obviousness.

The U.S.P.T.O. has the initial burden of demonstrating why one skilled in the art would have been motivated to make the proposed modifications needed to arrive at the presently claimed methods. The Office Action contends that "the instant claims read on reference compounds and the specific compounds recited in the remaining claims are structural analogs that fall within the genus taught by the reference". Applicants respectfully submit that, as pointed out above, the compounds defined by the present claims do not fall within the scope of Tsuda et al.'s disclosure. As set forth in applicants' Response to Office Action filed on December 16, 2005, which is incorporated herein as if set forth at length, Tsuda lists over 800 compounds that are different from the compounds of the present invention. As set forth in applicants' Response to Office Action filed on December 16, 2005, which is incorporated herein as if set forth at length, there is no teaching or suggestion for further experimentation to derive the claimed compounds. According to case law, an obvious to try rationale, which seems to be the suggested basis for the rejection, is not sufficient to establish *prima facie* obviousness under 35 U.S.C. § 103. There must be "some objective suggestion or teaching" in the prior art to modify the reference. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). See also *In re Kotzab*, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1318 (Fed. Cir. 2000) (Court reversed obviousness rejection involving technologically simple concept because there was no finding as to the principle or specific understanding within the knowledge of a skilled artisan that would have motivated the skilled artisan to make the claimed invention); *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999) (The level of skill in the art cannot be relied upon to provide the suggestion to combine references.); *In re Lahu*, 223 USPQ 1257, 1259 (Fed.Cir.1984) ("[i]n determining whether a case of *prima facie* obviousness exists, it is necessary to

ascertain whether the prior art teachings would appear to be sufficient to one of ordinary skill in the art to suggest making the claimed substitution or other modification.”); *In re Jones*, 21 USPQ2d 1941, 1943 (Fed.Cir. 1992) (“Conspicuously missing from this record is any evidence, other than PTO’s speculation ... that one of ordinary skill ... would have been motivated to make modifications of the prior art ... necessary to arrive at the claimed [invention].”); and *In re Grabiak*, 226 USPQ 870, 872 (Fed.Cir.1985) (“there must be adequate support in the prior art...in order to complete the PTO’s prima facie case and shift the burden of going forward to the applicant.”).

At pages 5 and 6 of the Office Action, the only support for the obviousness rejection is the Office Action’s recital that the instant claims read on reference compounds and the specific compounds recited in the remaining claims are structural analogs that fall within the genus taught by the reference. No recital of an objective suggestion or teaching in the prior art to make the modifications set forth in the claims of the present invention are provided in the Office Action whatsoever.

Applicants respectfully submit that the presently rejected claims are unobvious and patentable over the prior art. Accordingly, applicants respectfully request the withdrawal of the above-discussed Section 103 rejections.

Rejections under the judicially created doctrine of obviousness-type double patenting

Claims 61-63, 66-69, 81-83 and 85 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting in view of U.S. Patent 6,706,720.

Applicants respectfully traverse the rejection for the reasons of record, which are incorporated herein as if set forth at length, namely, that as a matter of law, the imposition of a double patenting rejection of this type is improper given that this application is filed as a divisional application (resulting from a restriction requirement imposed by the Office) of the application which matured into U.S. Patent 6,706,720.

The Office Action indicates that applicants’ arguments have been fully considered but were not found to be persuasive in that during prosecution applicants filed a narrower subgenus, which issued as U.S. Patent 6,706,720, that overlaps the genus of the rejected claims.

Assuming *arguendo* that the Office Action accurately describes the genus of U.S. Patent 6,706, 720 and the instant claims as overlapping, applicants respectfully submit that current statutory law prohibits the use of U.S. Patent 6,706,720 as a reference against the instant application.

35 U.S.C. §121 states the following:

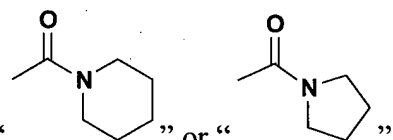
A patent issuing on an application with respect to which a requirement for restriction under this section has been made, or on an application filed as a result of such a requirement, ***shall not*** be used as a reference either in the Patent and Trademark Office or in the courts against a divisional application or against the original application or any patent issued on either of them, if the divisional application is filed before the issuance of the patent on the other application.

Because U.S. Patent 6,706,720 issued on an application with which a requirement for restriction under §121 was made and the instant divisional application was filed before issuance of U.S. Patent 6,706,720, applicants respectfully submit that 35 U.S.C. §121 prohibits that use of U.S. Patent 6,706,720 as a reference against the instant divisional application. Accordingly, applicants respectfully request that this judicially created doctrine of obviousness-type double patenting rejection be withdrawn.

Rejections under 35 U.S.C. §112, second paragraph

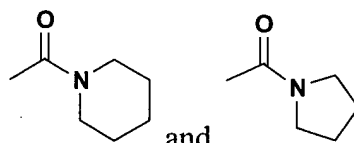
Claim 84 stands rejected under 35 U.S.C. §112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Office Action contends that there is insufficient antecedent

basis in claim 61 on which claim 84 depends for the limitation R^{3*} is “
because claim 61 excludes these substituent groups.



Without acceding to the correctness of that contention, in order to expedite the prosecution of this application, applicants have amended claim 84 to overcome the aforementioned rejection. In

particular, claim 84 has been amended such that
no longer appear in the claim. Because the Section 112, second paragraph, rejection has been rendered moot by the aforementioned amendment, applicants respectfully request withdrawal of this rejection.



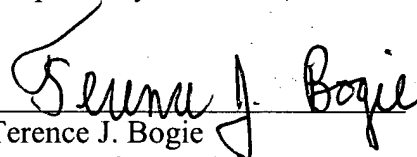
Conclusion

The presently submitted amendment and remarks are believed to be fully responsive to the rejections noted in the outstanding Final Office Action. Accordingly, applicants respectfully submit that the pending claims are in condition for allowance. An early Office Action to that effect is, therefore, earnestly requested.

The Commissioner is hereby authorized to charge any fees that may be required, including any fees under 37 C.F.R. §§1.16 and 1.17, for the filing of this paper to Deposit Account No. 19-3880.

If, in the opinion of the Examiner, a telephone conference with the undersigned would facilitate prosecution of this patent application, the Examiner's call would be welcomed.

Respectfully submitted,



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